Do tumor location and grade affect survival in pT2N0M0 esophageal squamous cell carcinoma?

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Background: The TNM staging system for esophageal cancer in the seventh edition of the *AJCC Cancer Staging Manual* incorporates tumor grade and location for staging pT2-3N0M0 esophageal squamous cell carcinoma. Patients with pT2N0M0, classified as stage IIA according to the sixth edition of the *AJCC Cancer Staging Manual*, can now be classified as stage IB, IIA, or IIB. We discuss whether these changes lead to a better prediction of the prognosis of these patients and aimed to find out other factors to forecast patient prognosis.

Methods: We retrospectively analyzed 317 patients with postoperative pathologic stage T2N0M0 who underwent esophagectomy between 1990 and 2005 at Sun Yat-sen University Cancer Center. We performed univariate and multivariate analyses to identify prognostic factors for survival and used the Kaplan–Meier method to demonstrate the prognostic efficacy of each prognostic factor, including tumor grade and location.

Results: The 5-year overall survival was 57%, with a median survival of 84.5 months (6.94 years). Univariate analysis indicated that age, alcohol consumption, and tumor grade were associated with survival. Multivariate Cox proportional hazard regression analysis revealed that alcohol consumption and tumor grade were independent prognostic factors. Survival analysis using the Kaplan–Meier method demonstrated age, cigarette smoking, alcohol consumption, tumor grade, and location as prognostic factors.

Conclusions: For pT2N0M0 esophageal squamous cell carcinoma, the seventh edition of the *AJCC Cancer Staging Manual* does not provide a more distinguishable prediction of prognosis compared with the sixth edition. Tumor grade is an independent prognostic factor in patients with pT2N0M0 esophageal squamous cell carcinoma, whereas tumor location is not. Furthermore, alcohol consumption is an independent prognostic factor that may imply a worse prognosis. (*J Thorac Cardiovasc Surg* 2013;146:45-51)

Esophageal squamous cell carcinoma (ESCC) has a poor prognosis and is one of the most common and aggressive cancers found throughout Asia, especially in China.^{1,2} Surgery is the main treatment, but the overall survival remains unsatisfactory. Half of those patients had potentially curative resections with a 3.5-year survival of 41.3%; for those resected for palliation, the 3.5-year survival was 7.3%. The overall survival remains at 20% to 25%.³

Accurate cancer staging is important for formulation of treatment protocols, therapeutic evaluations, and assessment of prognosis. In addition, it allows for treatment comparisons between different centers. The seventh edition of

the *AJCC Cancer Staging Manual* was released in 2010,⁴ updating the TNM staging system for esophageal cancer. In this manual, tumor location is simplified and includes the esophagogastric junction and proximal 5 cm of the stomach. Furthermore, T classifications are redefined and T4 is subclassified. Regional lymph nodes are redefined, and N is subclassified according to the number of regional metastatic lymph nodes. M is redefined, and stages are separated for squamous cell carcinoma and adenocarcinoma. Stages are reassigned using the T, N, M, and G classifications.⁴

T2N0M0 ESCC was previously classified as stage IIA according to the sixth edition of the *AJCC Cancer Staging Manual*,⁵ but it can now be classified as stage IB, IIA, and IIB according to the seventh edition. We retrospectively analyzed 317 patients with T2N0M0 ESCC who underwent esophagectomy to investigate whether the new stage classification meant varied prognosis and whether any other factors affected survival.

PATIENTS AND METHODS

Patient Data Acquisition

This study was approved by the Sun Yat-sen University Cancer Center Hospital Ethics Committee. All patients who underwent esophagectomy for esophageal cancer at the Thoracic Surgery Department of Sun Yat-sen University Cancer Center from 1990 to 2005 were reviewed. Among

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Abbreviation and Acronym

ESCC = esophageal squamous cell carcinoma

them, 317 who had pT2N0M0 ESCC and underwent curative (R0) resection were included in this study. All tumors were located in the thoracic segments, and no patient received neoadjuvant chemotherapy or radiotherapy.

Clinical Data

The study included 317 patients with T2N0M0 ESCC (222 male and 95 female) and a median age of 56 years (mean age, 55.6 years; standard deviation, 9.774) who underwent esophagectomy between 1990 and 2005. Of these, 186 patients (58.7%) smoked cigarettes and 60 patients (18.9%) consumed alcohol (a drinker refers to those who drink >100 g/d for >1 year.). In regard to tumor location, 40 (12.7%) were in the upper thoracic region, 218 (69.0%) were in the middle thoracic region, and 58 (18.4%) were in the lower thoracic region. According to tumor grade, 121 (38.3%) were well differentiated (G1), 126 (39.9%) were moderately differentiated (G2), and 69 (21.8%) were poorly differentiated (G3). The 1-, 3-, and 5-year overall survivals were 75%, 63%, and 57%, respectively, with a median survival of 84.5 months (6.94 years). Patient characteristics are summarized in Table 1.

Tumor Location

In this study, the medical records were accomplished before the publication of the seventh edition of the *AJCC Cancer Staging Manual*,⁴ so the relationship between the exact location of tumor and the new landmarks was not recorded. However, the distance from the tumor to the superior incisor has been measured by endoscopy and recorded in detail, and thus can be used to estimate the location of tumor. A tumor 15 to 20 cm away from the superior incisor was considered as cervical, whereas tumors 20 to 25 cm, 25 to 30 cm, and 30 to 40 cm were considered upper thoracic, middle thoracic, and lower thoracic, respectively.

Statistical Analysis

All potential and reported prognostic factors, including demographic data, cigarette smoking, and alcohol consumption; operative information; and tumor characteristics were analyzed. Patient data were evaluated according to pathologic stage classification of the sixth edition of the *AJCC Cancer Staging Manual*.⁵ Cervical, upper thoracic, middle thoracic, and lower thoracic were coded as 1, 2, 3, and 4, respectively, when tumor location was involved in the analysis. In terms of differentiation grade, tumors that were highly, intermediately, and poorly differentiated were coded as 1, 2, and 3, respectively.

Follow-up

Postoperative patients were followed regularly at our outpatient department every 3 months in the first 2 years after operation, every 6 months in the third year, and once per year in the following 2 years. Outpatient department visits encompassed history taking, physical examination, chest x-ray, barium meal, abdominal type B ultrasonography, and tumor biomarkers, including squamous cell carcinoma and carcinoembryonic antigen. Endoscopic examination and computed tomography were carried out on occasion. Patients with survival time more than 5 years were contacted by our follow-up department via telephone or mail. Overall survival was defined as the time from operation to death or the last follow-up. The last follow-up checkpoint was April 2010. Fourteen of 317 patients were lost to follow-up.

Statistics

Overall survival was calculated on the basis of survival time from operation to death or the last follow-up. Life table analysis was used to calculate

the 1-, 3-, and 5-year overall survival. Univariate analysis and multivariate Cox proportional hazard regression analysis were used to identify potential prognostic factors. Potential prognostic factors associated with survival probability that had a significance level of P less than .10 were considered in multivariable Cox proportional hazard regression analysis. Patient survival curves were constructed using the Kaplan–Meier method. The log-rank test was used to compare survival differences between groups for each variable. All statistical calculations were performed using the Statistical Package for the Social Sciences version 17.0 (IBM SPSS Inc, Chicago, Ill).

RESULTS**New Criteria for Staging**

The 317 patients with pT2N0M0 ESCC were divided into 3 subgroups, namely, IB, IIA, and IIB, according to the seventh edition of the *AJCC Cancer Staging Manual*.⁴ Kaplan–Meier analysis revealed no significant differences between the survival curves for each group. P value calculated by the log-rank test was .305, which indicated that the 3 subgroups resulting from the new criteria did not have a significantly different prognosis. The seventh edition did not provide a more distinguishable prediction of patients with pT2N0M0 ESCC (Figure 1).

Prognostic Factors

Prognostic factors affecting long-term survival are evaluated in Tables 2 and 3. Univariate analysis indicated that age ($P = .038$), alcohol consumption ($P = .035$), and tumor grade ($P = .007$) were significantly associated with patient survival. Likewise, multivariate Cox proportional hazard regression analysis indicated that alcohol consumption ($P = .015$) and tumor grade ($P = .011$) were significantly associated with patient survival (Table 3).

The Kaplan–Meier method and log-rank test were used to construct survival curves for age, alcohol consumption, and cigarette smoking. The cutoff point for age was defined at the median age of 56 years. However, age as a continuous variable was not dichotomized elsewhere. Age ($P = .029$), alcohol consumption ($P = .028$), and cigarette smoking ($P = .039$) were observed to be significantly associated with patient survival (Table 3). Furthermore, advanced age, cigarette smoking, and alcohol consumption were associated with worse prognosis (Figure 2).

Role of Tumor Grade and Location in Esophageal Squamous Cell Carcinoma

Univariate analysis and multivariable Cox proportional hazard regression analysis indicated that tumor grade was associated with patient survival ($P = .007$ and $P = .011$, respectively) (Tables 1 and 2). We also established the survival curves using the Kaplan–Meier method, which indicated that well-differentiated tumors had better prognosis (Figure 3). For tumor location, to exclude the effect of tumor grade, we also established the survival curves of different tumor location in each grade. For moderately and

TABLE 1. Baseline characteristics of patients

Variables	No. (%) or median
Age, y	56
Gender	
Male	222 (70.0%)
Female	95 (30.0%)
Cigarette smoking	
Yes	186 (58.7%)
No	131 (41.3%)
Alcohol consumption	
Yes	60 (18.9%)
No	257 (81.1%)
Family history of cancer	
Yes	26 (8.2%)
No	291 (91.8%)
Surgical approach	
Left thoracic	249 (78.5%)
Right thoracic	68 (21.5%)
Tumor location	
Upper thoracic	40 (12.7%)
Middle thoracic	218 (69.0%)
Lower thoracic	58 (18.4%)
Tumor grade	
Well differentiated (G1)	121 (38.3%)
Moderately differentiated (G2)	126 (39.9%)
Poorly differentiated (G3)	69 (21.8%)

poorly differentiated pT2N0M0 ESCC, tumor location was not associated with patient survival ($P = .714$ and $P = .227$, respectively) (Figure 4). For the well-differentiated tumor,

FIGURE 1. Kaplan–Meier survival curves for patients staged by the seventh edition of the *AJCC Cancer Staging Manual*.⁴ Survival differences were analyzed using Cox regression analysis.

TABLE 2. Possible prognostic factors and relative risks

Possible prognostic factor	P	HR	95% CI
Gender	.606	1.187	0.619-2.273
Age	.038	1.023	1.001-1.045
Cigarette smoking	.263	1.360	0.794-2.329
Alcohol consumption	.035	1.570	1.032-2.389
Family history of cancer	.343	0.716	0.359-1.428
VC	.389	0.732	0.361-1.487
MVV	.267	1.009	0.993-1.026
FEV1	.956	1.024	0.434-2.420
FEV1%	.619	1.007	0.979-1.035
Blood loss	.725	1.000	0.999-1.001
3-FL	.223	0.647	0.322-1.302
Length of tumor	.372	1.043	0.951-1.143
Depth of tumor invasion	.516	1.131	0.780-1.639
Tumor grade	.007	1.373	1.091-1.728
Tumor location	.463	0.881	0.628-1.235
Postoperative anastomotic leakage	.379	1.381	0.673-2.835
Surgical approach	.215	1.461	0.802-2.661
No. of removed LNs	.938	0.999	0.969-1.030

HR, Hazard ratio; CI, confidence interval; VC, vital capacity; MVV, maximal voluntary ventilation; FEV1, forced expiratory volume in 1 second; FEV1%, forced expiratory volume in 1 s expressed as percent predicted; 3-FL, 3-field lymphadenectomy; LN, lymph node.

tumor location was linked with patient survival ($P = .006$) (Figure 4). Although the Kaplan–Meier method showed that tumor location was significantly associated with patient survival ($P = .015$), it was not identified as an independent prognostic factor in multivariable Cox proportional hazard regression analysis.

DISCUSSION

The seventh edition of the *AJCC Cancer Staging Manual*⁴ adopts evidence from evidence-based medicine and a new statistical model. For this revision, inputs from Asian scholars were invited because Asian countries have a higher incidence of ESCC, accounting for one third of patients with ESCC. The seventh edition incorporates tumor grade and location; however, these factors are less significant than TNM, which generally affects only the stage classification of patients with pT2-3N0M0. The new staging system specifically defines anatomic segmentation of esophageal cancer, considering the survival influence of organs adjacent to the tumors.

In the seventh edition of the *AJCC Cancer Staging Manual*,⁴ tumor location is redefined as the length between the upper incisor and the upper edge of the tumor, not the tumor center. The esophagus is now divided into cervical, upper thoracic, middle thoracic, and lower thoracic regions by 3 new landmarks, namely, the thoracic entrance, inferior border of azygos vein arch, and inferior border of inferior pulmonary vein.

In this study, the 5-year overall survival was 57%, which was in accordance with the data previously reported.

TABLE 3. Survival differences after multivariate Cox proportional hazard regression analysis

Demographics	Patient, no.	Univariate log-rank <i>P</i>	Multivariate regression <i>P</i>	HR	95% CI
Alcohol consumption		.028	.015	1.627	1.101-2.405
Yes	62				
No	240				
Age (y)		.029			
<56	60				
≥56	238				
Cigarette smoking		.039			
Yes	186				
No	131				
Tumor location		.015			
Upper thoracic	40				
Middle thoracic	218				
Lower thoracic	58				
Tumor grade		.015	.011	1.323	1.066-1.641
Well differentiated (G1)	121				
Moderately differentiated (G2)	126				
Poorly differentiated (G3)	69				

HR, Hazard ratio; CI, confidence interval.

Killinger and colleagues⁶ reported their experience with pathologic T2N0M0 disease treated using esophagectomy alone. In this retrospective analysis, the survival of patients with pT2N0M0 disease was on par with that of patients with pT1N0M0 (~50% at 5 years; $P = .83$) and trended toward improved survival over patients with pT3N0M0 disease ($P = .06$). Tachibana and colleagues⁷ published the results of their study on patients with pT1 and pT2 ESCC who underwent esophagectomy. Among patients who were node negative, those with pT1 and pT2 tumors had similar cancer-specific survival. Rice and colleagues⁸ reported that 31 patients with pT2N0M0 ESCC who underwent surgery first had a 5-year overall survival of $61\% \pm 9.3\%$.

We performed a survival analysis for 317 patients with pT2N0M0 ESCC. Univariate analysis showed that age, alcohol consumption, and tumor grade were associated with patient survival. Furthermore, multivariable Cox proportional hazard regression analysis revealed that alcohol consumption and tumor grade were independent prognostic factors. Cigarette smoking was found to be associated with patient survival using the Kaplan–Meier method.

The prognostic role of age has been demonstrated in many previous studies. It has been confirmed that advanced age is associated with worse prognosis. Elsayed and colleagues⁹ reported that increasing age was a significant risk factor for mortality and survival after esophagectomy. The mortality was particularly high when associated with a pre-operative cardiac or respiratory morbidity. Eloubeidi and colleagues¹⁰ showed that across all stages, age was an important predictor of survival in patients with esophageal carcinoma.

In regard to alcohol consumption, the predictive role on survival varies among studies. Kountourakis and colleagues¹¹ demonstrated that alcohol consumption

influences the long-term outcome of patients with cT2N0M0 esophageal cancer, although different opinions exist.¹² In our study, alcohol consumption was found to be strongly associated with poor survival.

Because cigarette smoking and alcohol consumption synergistically contribute to ESCC development,¹³⁻¹⁵ we evaluated smoking as a prognostic factor. Survival curves demonstrated that smoking is not only a risk factor for ESCC development but also a prognostic factor in patients already diagnosed with ESCC. Identical results were reported by Khan and colleagues¹⁶ in a cohort from the Kashmir Valley, India. Kountourakis and colleagues¹¹ showed that smoking influenced long-term outcome in patients with cT2N0M0 esophageal cancer, a conclusion confirmed by Shitara and colleagues.¹⁷

Univariate analysis, multivariate Cox proportional hazard regression analysis, and the Kaplan–Meier method showed that tumor grade had a significant influence on survival of patients with pT2N0M0 ESCC and was an independent prognostic factor, whereas tumor location was not.

Tumor grade was shown to be a prognostic indicator in perijunctional esophagogastric carcinoma long before the adoption of the new staging system¹⁸ and was incorporated in the new staging system¹⁹; however, its role in ESCC remains unclear.^{10,20,21} In a 292-patient study, Li and colleagues² showed that tumor grade was a prognostic factor in univariate analysis, but not in multivariate Cox regression analysis. Roder and colleagues²² reported that in squamous cell carcinoma–predominant databases, tumor differentiation was not significantly associated with survival.

Similar conflicting results have been obtained for tumor location.^{2,10,20} Although studies have shown that tumors in the lower segment of esophagus had better prognosis because of the increased sufficiency of resection, these

FIGURE 2. Kaplan–Meier survival curves for patients stratified by age (A), alcohol consumption (B), and cigarette smoking (C). Survival differences were analyzed using Cox regression analysis.

FIGURE 3. Kaplan–Meier survival curves for patients stratified by tumor grade (A) and location (B). Survival differences were analyzed using Cox regression model analysis.

studies included a large proportion of patients with adenocarcinoma of the distal intra-abdominal esophagus; therefore, the results may not reflect the exact effect of tumor location on thoracic ESCC prognosis.^{10,19} To study this issue further, Doki and colleagues²³ analyzed 501 patients with thoracic esophageal cancer (92% with ESCC). They reported that upper, middle, and lower thoracic esophageal cancers had similar 5-year disease-free survival, but the mode of tumor recurrence differed for each primary tumor location. We believe the fact that all of these patients with T2N0M0 had tumors that were contained within the wall of the esophagus may account for our results. T3 or higher tumors located in the lower chest are likely more amenable to wide resection with better margins than those

FIGURE 4. Kaplan–Meier survival curves for patients with well (A), moderately (B), and poorly (C) differentiated tumor stratified by tumor location. UT, Upper thoracic; MT, middle thoracic; LT, lower thoracic.

located in the upper chest. In this regard, tumor location is probably less important with T2N0M0 tumors.

However, none of these studies focused solely on patients with pT2N0M0 ESCC, the main group affected by the new G stage classification. In our study, we found that tumor grade was an independent prognostic factor, and a relatively poorer differentiation was associated with poor survival. Different tumor locations were associated with survival, but they may not be independent prognostic factors. This may be attributed to the impaired accuracy of tumor location during the conversion from the sixth⁵ to the seventh edition⁴ of the *AJCC Cancer Staging Manual*.

CONCLUSIONS

In addition to well-characterized factors affecting survival of patients with esophageal carcinoma, we showed that alcohol consumption and tumor grade were important prognostic factors for patient survival. Tumor grade was a strong prognostic factor in patient survival, as indicated in the seventh edition of the *AJCC Cancer Staging Manual*,⁴ whereas tumor location was not. The revised TNM staging system does not suggest a more efficient prediction of prognosis than the previous edition for patients with pT2N0M0 ESCC.

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